Paradigm Shift in the Regulatory Environment for Rapid Human Proof of Concept - Microdosing

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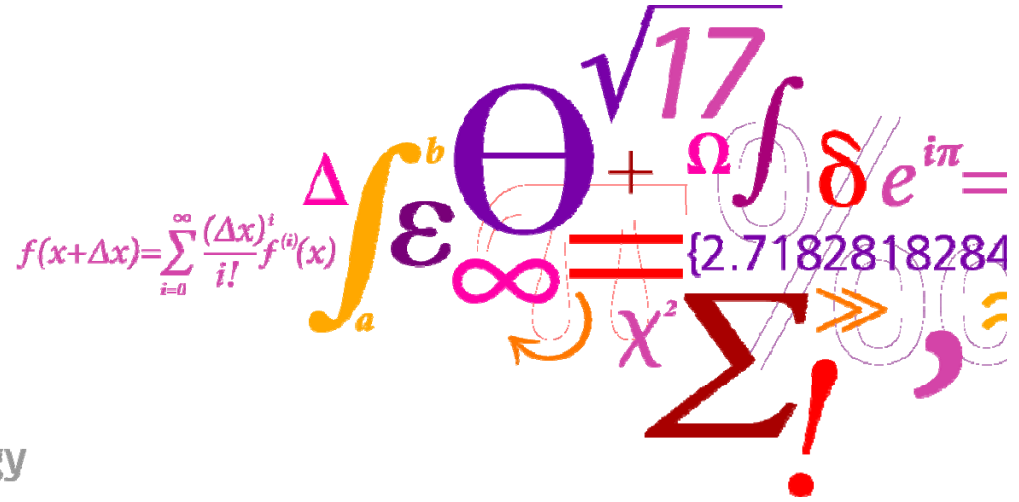
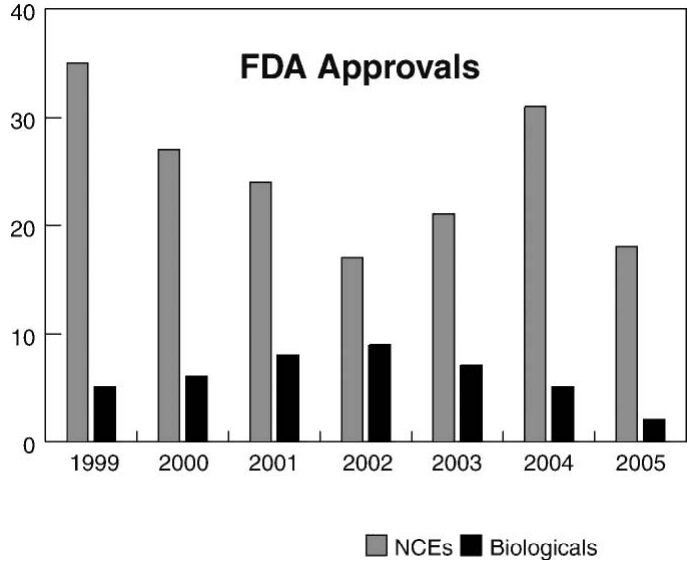


Risø DTU
National Laboratory for Sustainable Energy

- **The when, how and what of microdosing**
- **Technolocy behind (AMS and PET) and examples of microdosing studies.**
- **Validity of microdosing studies**
- **Perspectives for Controlled Release**
- **Conclusion**

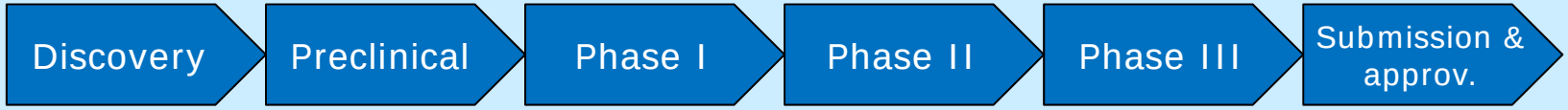
Many scientific breakthroughs in biology ! How about new drugs ?

- Human genome projects
- Proteomics
- Metabollomics
- High Throughput screening
- Improved *in silico* techniques.



CT Caskey, Annu. Rev. Med. 2007. 58:1–16

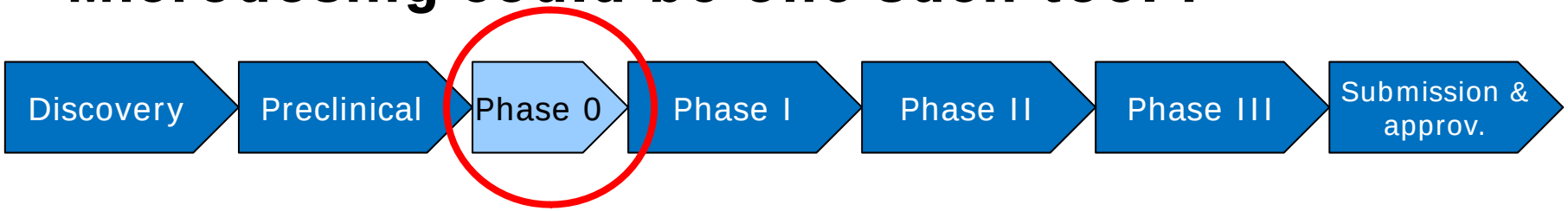
The Pharma-challenge:



- Overall time from discovery to approval of approx. 12 years
- Estimated cost for pharmaceutical development of $ 1 billion
- Patent protection only applies for 20-25 years.
- Only 1 out of 5 to 1 out of 10 drugs reach the market
- Approximately 40% attrition due to unsuitable pharmacokinetics or metabolism
- Preclinical testing requires extensive and lengthy tox evaluations

A need for 21st century tools for 21st century pharmaceutical development (FDA, critical path document)

Microdosing could be one such tool !



Phase 0

- Injection of drug compound in the microgram range.
- Due to the low dose, no pharmacological response expected and less animal testing for toxicology needed.
- Early acces to pharmacokinetics and pharmacodynamics

Bergström et al, *Eur. J. Clin. Pharmacol,* **2003**, 357

Lappin et al, *Nature Reviews in Drug Discovery*, **2003**, 233

Microdosing – The industry perspective

- Reduced time from PLC to Human administration
  - Without microdosing, 12-18 months
  - With microdosing, 4-8 months.
- More compounds testet in humans
  - Usually several preclinical leads
  - Most promising leads may be taken to clinick in parallel.
- Potential to ”kill” unsuccessful PLC’s quickly and reduce overall costs.
- Human pharmacokinetics and pharmacodynamics as basis for stop/go decisions.
- Additional cost reductions due to reduced Tox-packages and reduced requirements to drug products amounts and quality.

The Regulators Perspective

- Potential as an important tool in speeding up drug development process and reduce costs.
- Critical to ensure test subject safety
- Potential in reducing the use of test animals for safety and tox studies.

- EMEA white paper, 2004. ”Position paper on non-clinical safety studies to support clinical trials with a single microdose”
- FDA guidance for industry, eIND in 2006. ”Guidance for Industry, Investigators and Reviewers, Exploratory IND studies”.

Regulations for microdose studies

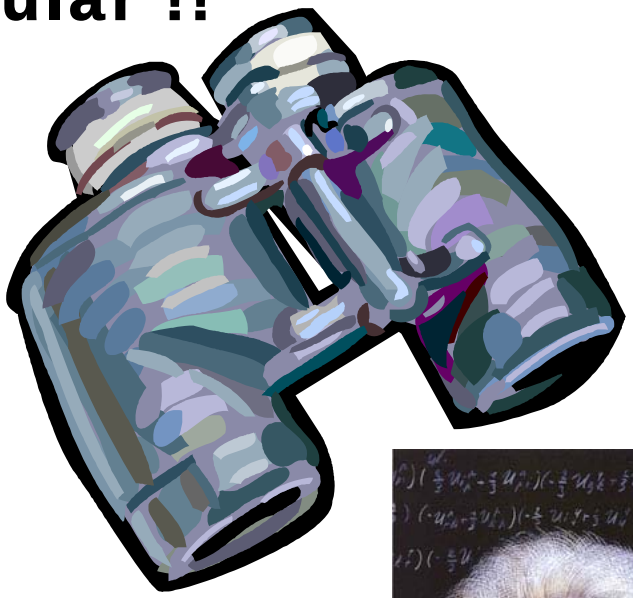
- **Small amounts of drug product administered:**
  - 1/100th of the dose calculated to give a pharmacological response.
  - Maximum 100 µg
  - Maximum 30 nmoles for protein products (FDA)
- **Extended single dose studies to asses toxicology**
  - One mammalien species when justified
  - Study should establish a dose inducing a minimal toxic effect.
  - Alternatively, for drugs with low toxicity, a safety margin of 100 and 1000 is required by FDA and EMEA respectively.
- **Genotoxicity studies**
  - EMEA requires test for genotoxicity
  - FDA requires no routine genetic toxicology test

But, are genotoxicity studies necesarry ??

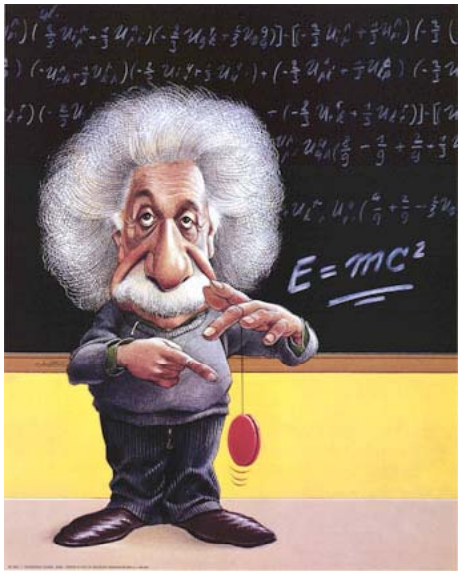
- EMEA/CHMP/SWP/5199/02
  - For"Safe" chemical structures,- impurities < 1,5 µg/day may be discarded for genotoxicity (Treshold for toxocological concern (TTC))
  - For structures with genotoxic structures, impurities <0.15 µg/day may used as TTC
  - For products with short term administration, TTC could be higher.
- PhRMA white paper
  - Agrees with TTC of 1.5 µ/day
  - Suggest a limit of 120 µg/day for short interval administration.
- For PET examinations, genotoxic potential of radiation 10-100 times higher than that of the administered chemical.
- Suggested that for microdosing studies, genotoxicity studies not obligatory.

H Lundquist, G Antoni, B Långstrøm, *Eur J Clin Pharmacol.* (**2007**), 641

But, to study the fate of < 100 µg – you need to use the large binocular !!



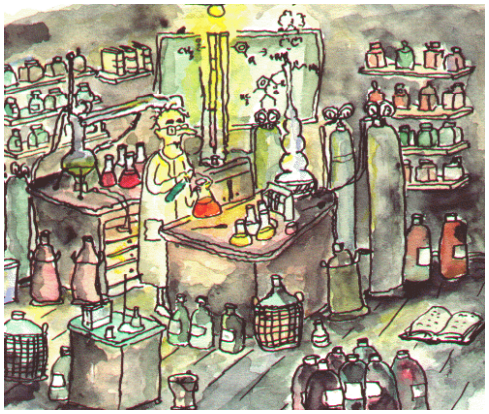
- 40 femtomol/ml if evenly distributed in blood (5 l)
- 2.9 femtomol/ml if evenly distributed in body fluid (70 l)



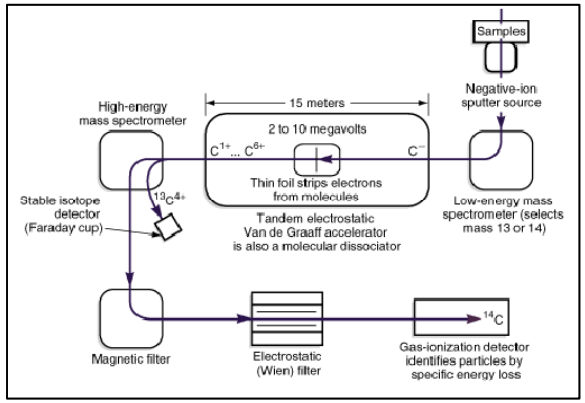
You need femto – atto molar sensitivity

- Accelerator Mass Spectroscopy (AMS)
- Positron Emission Tomography (PET)

The AMS study



- Requires GMP (or GLP) manufacture of 14C-labelled drug product.
- Typically intravenous injection of drug product as well as intended route of administration.
- Typically less than 50 nCi 14C-drug administered (1.85 kBq)
- Drawing of blood samples, urine etc. for AMS sampling.
- After sample preparation and compound separation, collected samples are subjected to AMS



An example of an AMS study

- α_{1A}-Adrenoceptor antagonist
- Injection of 50 nCi C-14 labelled Drug product (5 µg, 50 µg and 500 µg)
- Collection of blood samples (>100 h) and urine samples (72 h)

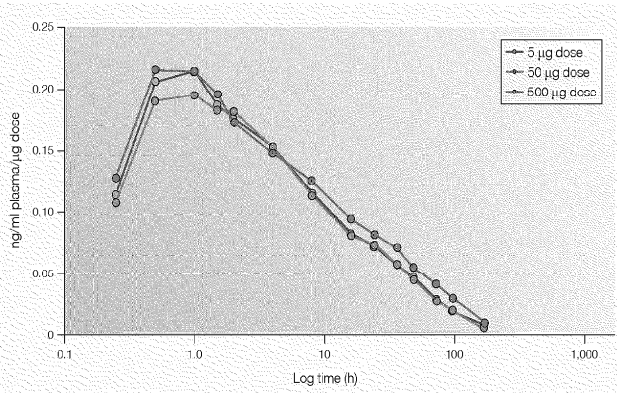


Figure 2 | **Semi-log plot comparing elimination of drug from plasma following a 5, 50 or 500 µg oral dose at a constant radioactive dose level of 50 nCi per subject.** The plot shows linear kinetics across the dose range[24].

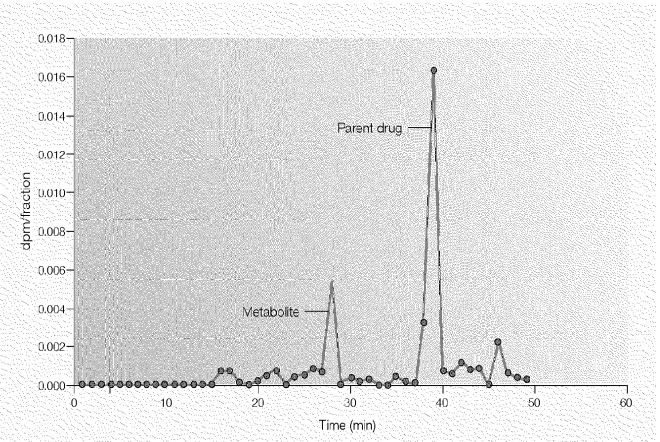


Figure 3 | **Example of a drug metabolite profile from a plasma extract.** Note that the metabolite peak equates to only 0.006 disintegrations per minutes (dpm). In this example, 0.02 dpm were injected on the column[31].

G. Lappin, RC Garner, *Nature Reviews in Drug Discovery*, **2003**, 233

The PET approach

Manufacturing sites:

GMP or GMP-like production

18F- og 11C tracers with high specific activity.

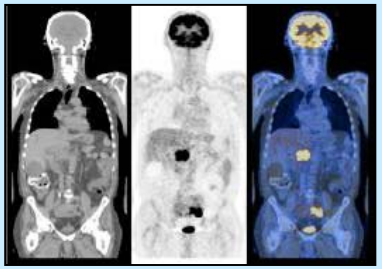
Highly specialised staff (Physics, chemistry and pharmacy)

Clinical sites:

Usually hospital based with PET(/CT)

Should have in-house blood analysis capabilities.

Highly specialised staff (medicine, physics, chemistry)



Example of a PET study – 18F Ciprofloxacin

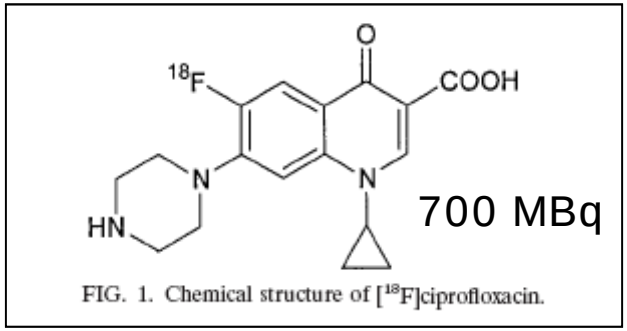
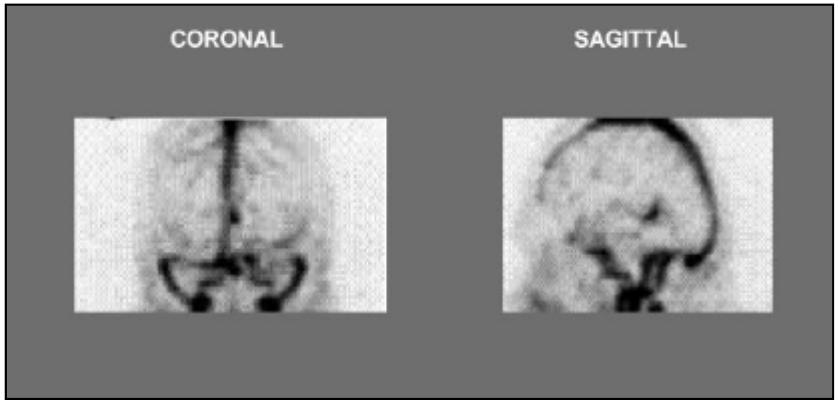
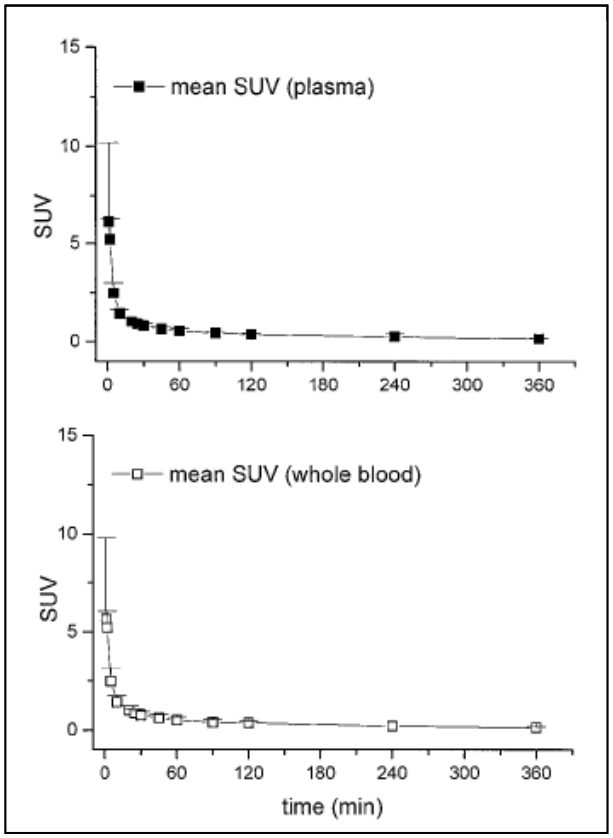


FIG. 1. Chemical structure of [^{18}F]ciprofloxacin.

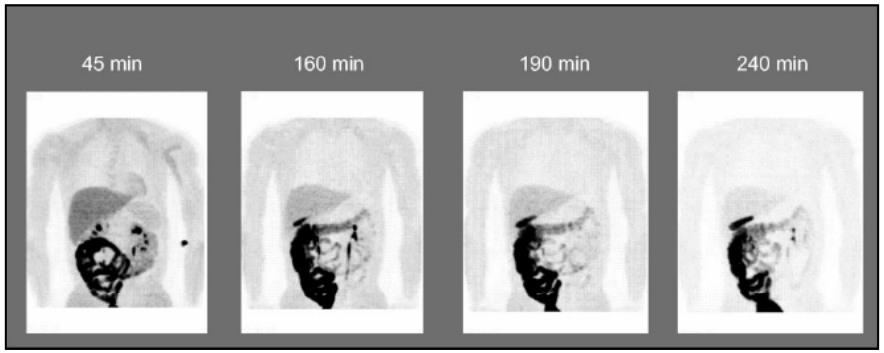


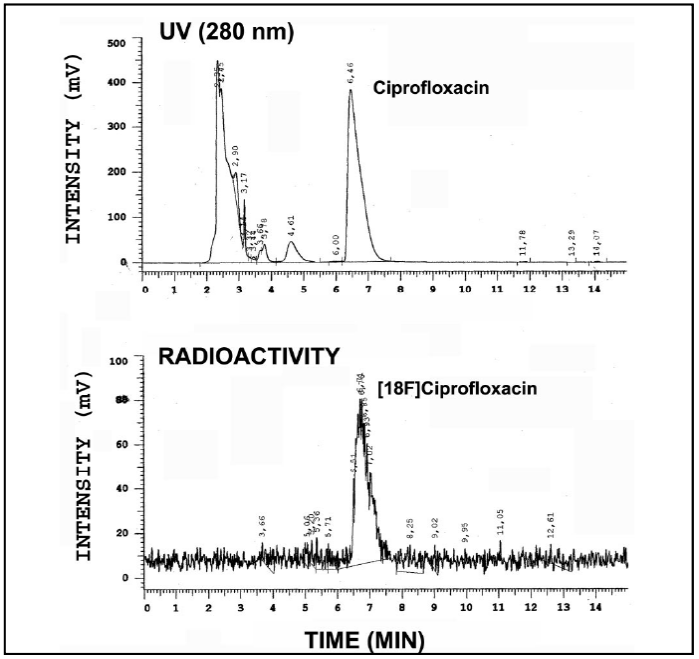
0-30 min Post injection

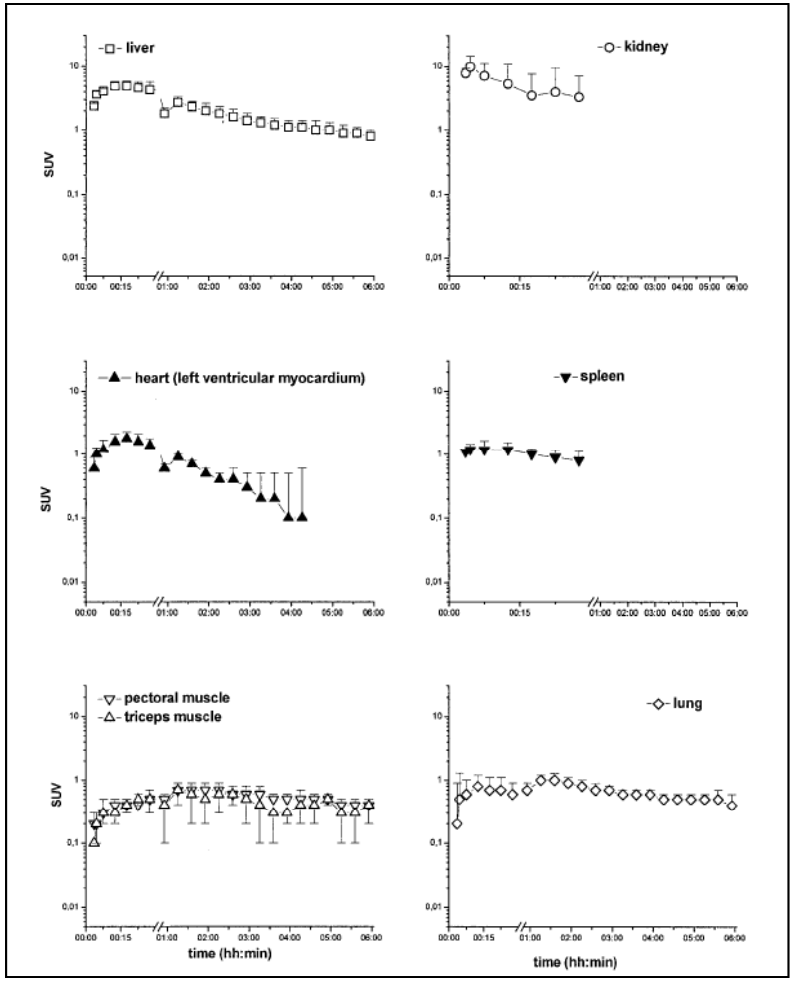


M Brunner et al, *Antimicrob Agents Chemother*, **2004**, 3850

18F-Ciprofloxacin cont.







M Brunner et al, *Antimicrob Agents Chemother*, **2004**, 3850

But ! Is microdosing truly representative ?

- Is scaling from microdoses to therapeutic doses linear ?
- Nonlinearity could be induced by saturations of:
  - binding to target
  - Affinity to other systems
  - Metabolism
  - Elimination pathways.
- If not scaleable, high risks of misinterpretations.

Recent studies confirm an approximate linearity

- CREAM study (Consortium for Resourcing and Evaluating AMS Microdosing)
  - Five drugs known for difficult human PK prediction studied
  - Dosing at microdose and therapeutic dose levels
  - Approximately 70% correspondance.

- EUMAPP (European Microdosing AMS Partnership Programme)
  - Seven drugs with problematic predictive models for PK
  - Assesment of pharmacokinetic linearity from micro- to therapeutic dose
  - For all drugs, IV microdoses predicted t½, CL and V very well.
  - Oral data did not scale as well but could be explained from chemical and metabolic properties.

CREAM: RC Garner, *Drug Discovery Today*, **2005**, 449

EUMAPP: http://www.eumapp.com/

AMS & PET approach – which is the better ?

- Both will provide initial pharmacokinetic data and values enabling the estimation of t½, clearance (CL) and distribution volumes (V).
- Both have shown to give data from microdosing that are representative for the therapeutic dose levels (within a factor of 2)
- Both provide an oppertunity to obtain early data to support decision making in preclinical and early clinical trials.

- AMS gives the oppertunity of investigating drugs with long biological half-lives.
- AMS is less expensive and generally faster to set up

- PET gives the oppertunity of additional tissue distributions and kinetics. PET therefore provides early indications of pharmacodynamic properties.

It depends on your question – they compliment each other

Microdosing and Controlled release – Perspectives from an outsider !

CR is about the delivery more than about the active compound.

Potential for microdosing in the investigation of CR effects

- Sustained release
- Bioavailability
- Prodrugs

Great potential for microdosing and PET imaging for investigation of targeting effects.

- Targeting of API with carrier – does it deliver
- ADME information for API/Carrier
- (Receptor binding studies/occupancy)

But – will your carrier/formulation etc. be MICRO ??

In Conclusion

Microdosing is a valuable tool in the very early phases of clinical development.

The approach is accepted by authorities and adequate scientific proof has been provided.

AMS and PET are both valuable tools in microdosing. Which to use depends on the question asked as the compliment each other.

Microdosing with PET or AMS has potential also in the investigation of controlled release investigations.

To learn more ….

- Positron emission tomography microdosing: a new concept with application in tracer and early clinical drug development, Bergström et al, *Eur. J. Clin. Pharmacol,* **2003**, 357
- Positron Emission tomography for use in microdosing studies, Wagner et al, *Current Opinions in Drug Discovery & Development,* **2008**, 104
- Outcomes from EUMAPP – A study comparing *in vitro, in silico,* microdose and pharmacological dose pharmacokinetics. *www.eumapp.org*
- Use of microdosing to predict pharmacokinetics at the therapeutic dose: Experience with 5 drugs, Lappin et al, *Clinical Pharmacology & Therapeutics*, **2006**, 203
- Big Physics, small doses: The use of AMS and PET in human microdosing of development drugs, Lappin et al, *Nature Reviews in Drug Discovery*, **2003**, 233
- The utility of microdosing over the past 5 years, Lappin et al, *Expert opin. Drug Metab. Toxicol.* **2008**, 1499
- Improved early clinical development through human microdosing studies, Wilding & Bell, *Drug Disc. Today*, **2005**, 890

- Guidance for Industry, Investigators and Reviewers, Exploratory IND studies, FDA, **2006**
- Position paper on non-clinical safety studies to suppport clinical trials with a single microdose, EMEA, **2004**